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10/530,108	04/01/2005	Silvia Trasciatti	NOTAR4.001APC	2649

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
02/20/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,108	TRASCIATTI ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,10,11,13-15,25,26 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-8,10,11,13-15,25,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 11/12/08 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/12/08 has been entered.

Claims 1, 5-6, 10, 13-15, and 28 have been amended.

Claims 12, 17-18, and 27 have been cancelled.

Claims 1, 5-8, 10-11, 13-15, 25-26, and 28 are pending and are under examination.

2. The rejections of the claims under 35 U.S.C. 112 second paragraph are withdrawn in view of Applicant's amendment to the claims.

3. The rejection of the claims under 35 U.S.C. 112 first paragraph is withdrawn in view of Applicant's amendment to the claims.

4. The rejection of the claims under 35 U.S.C. 103 is withdrawn in view of Applicant's amendment to specify adding a corresponding volume of medium. However, Applicant's arguments relevant to the new grounds of rejection will be addressed below.

5. The following are new grounds of objection and rejection.

6. Claim 13 is objected to for the following informalities: The claim recites collecting the TALL-104 cells into "frozen bags". However, it would be more accurate if the claim recited collecting the cells into bags and freezing the bags.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "he harvest time" in line 2. There is insufficient antecedent basis for this limitation in the claim, or in independent claim 1.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 5-8, 10-11, 13, 15, 25-26 and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/26284 (of record), in view of Gambacorti-Passerini et al. (of record), Tuyaerts et al. (of record), and Schumpp et al., 1990, as evidenced by the product information for Nunc cell factories (of record).

WO 94/26284 teaches that TALL-104 lymphocytes are an immortal killer cell line that permanently and rapidly grow in the presence of IL-2 in vitro (see page 19, in particular). WO 94/26284 further teaches a process for amplifying TALL-104

lymphocytes comprising growing the cells in the presence of IMDM medium supplemented with 10% fetal bovine serum and IL-2 (i.e. an antibiotic free medium). WO 94/26284 further teaches adding fresh medium containing IL-2 on a biweekly basis, which results in the continuous growth of TALL-104 cells in a exponential fashion. WO 94/26284 also teaches growing the TALL-104 cells with 100 U/ml of IL-2 (see page 24 in particular). WO 94/26284 also teaches using TALL-104 cells that have been modified by gamma irradiation, which results in loss of ability to synthesize DNA and RNA (i.e. "genetically" modified TALL-104 cells, see page 22 in particular). WO 94/26284 also teaches that the TALL-104 lymphocytes can be used for adoptive transfer therapy in humans (see page 18 and 38 in particular).

WO 94/26284 does not teach amplifying the cells in a 10 chamber stack, freezing the cells, or a medium comprising human serum.

Gambacorti-Passerini et al. teach a method for the large scale production of lymphocyte killer cells comprising culturing the cells at a concentration of 1.5×10^6 cells/ml in a 10 floor multi-chamber stack (Nunc Cell Factories™, see page 524 in particular). Gambacorti-Passerini et al. also teach that the killer lymphocytes can be grown in range of concentrations (2.5%, 5% or 10%) of homologous human serum without affecting cell recovery (see page 525 in particular). Gambacorti-Passerini et al. also teach harvesting the lymphocytes into bags, and freezing the bags (see page 524-525 in particular). Gambacorti-Passerini et al. also teach that the large scale production of the killer cells in the multi-chamber stacks results in fully comparable activation and function of the cells compared to cells grown in standard flasks (see page 527 in particular). Gambacorti-Passerini et al. also teach that the culture method using the multi-chamber stacks is faster and more affordable than other cell culture methods (see page 529 in particular).

Tuyaerts et al. teach that cytokine dependent cells can be grown in multi chamber stacks (Nunc Cell Factories™) by adding the cells in an initial volume of 160 mls of cytokine containing medium per chamber, followed by supplementing the cells with 25 mls of complete medium containing cytokines every 48 hours after the initiation of the culture (see page 138 in particular).

Schumpp et al. teach that the amplification of cells in culture results in depletion of nutrients and the accumulation of toxic components (see page 639, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to grow the TALL-104 cells of WO 94/26284 using a multi-chamber stack, as taught by Gambacorti–Passerini et al. and Tuyaerts et al. The ordinary artisan would be motivated to grow the TALL-104 cells in a multi chamber stack, since Gambacorti-Passerini et al. teach that it is faster and more affordable than other cell culture methods. Furthermore, it would have been obvious to add the TALL-104 cells to the multi-chamber stack in a volume as of 160 mls/chamber, as taught by Tuyaerts et al., followed by adding a volume of medium with IL-2 on a biweekly basis, as taught by WO 94/26284. The ordinary artisan would be motivated to add the fresh medium comprising IL-2, since WO 94/26284 teaches that addition of said medium results in the continuous and exponential growth of TALL-104 lymphocytes. Additionally, it would have been obvious to optimize the volume added, and the amounts recited in the instant claims are well within the purview of the ordinary artisan. The instant claims require addition of a volume of medium "corresponding to" the volume contained in the multichamber stack (i.e. a volume similar to that contained within the stack). Tuyaerts et al. teach adding an initial volume of 160 mls, and adding subsequent volumes of 25 mls. However, it would have been obvious to optimize the method by increasing the volume of medium added, since the growth of cells in culture results in a loss of nutrients and an accumulation of toxic components (see Schumpp et al., 1990). Thus, it would have been obvious to increase the amount of medium added to increase the essential nutrients and further dilute out any toxic components in the cultures. Furthermore, it would have been obvious to increase the volume added only to a certain point (i.e. not more than that contained in the multi chamber stack), since adding too high of a volume would result in the chamber becoming too full before a sufficient number of cells could be grown. Additionally, it would have also been obvious to optimize the initial volume added to the chamber by decreasing said volume, in order to allow more medium to be added in subsequent cytokine additions without the chamber becoming to full to quickly.

Additionally, the ordinary artisan would have a reasonable expectation of success in growing the TALL-104 lymphocytes in a multi-chamber stack, since Gambocorti-Passerini et al. teach that killer lymphocytes can be grown in said chambers, and Tuyaerts et al. teach that said chambers are amendable to addition of fresh medium containing cytokines. Furthermore, it would have been obvious to add the cells at a density of 1.5×10^6 cells, since Gambacorti-Passerini et al. teach that such a concentration is suitable for growing killer lymphocytes in a multi chamber stack. Additionally, the ordinary artisan would have had a reasonable expectation of success in amplifying the TALL-104 lymphocytes to obtain at least 1×10^9 cells, since WO 94/26284 teaches that TALL-104 lymphocytes expand exponentially when grown in IL-2. Furthermore, as evidenced by the Nunc product information for a multi-chamber stack, a 10 chamber stack is 335mm x 205mm x 190 mm (i.e. has a final volume capacity of ~13 L). Therefore, adding the inoculum at 160mls/chamber, or a total of 1.6 L for 10 chambers, as made obvious by WO 94/26284, Gambocorti-Passerini et al., and Tuyaerts et al., would correspond to ~1/8 of the total final volume capacity of the chamber. Moreover, the ordinary artisan would have been motivated, and have a reasonable expectation of success in substituting the homologous human serum taught by Gambacorti-Passerini et al. for the fetal bovine serum taught by WO 94/26284 et al., since the cells of WO 94/26284 et al. are used for human therapy, and homologous serum would be expected to be to avoid any potential for an adverse response to foreign bovine proteins in human patients. Additionally, it would have been obvious to perform a pre-expansion of the TALL-104 killer cell lines taught by WO 94/26284 to obtain the appropriate number of cells for inoculating the multi-chamber stack. Additionally, it would have been obvious to freeze the TALL-104 lymphocytes to provide a convenient and ready to use population of cells, and the ordinary artisan would have had a reasonable expectation of success, since Gambacorti-Passerini et al. teach that killer lymphocytes can be harvested from a multi chamber into bags and frozen.

Applicant's arguments filed 11/12/08 have been fully considered, but they are not persuasive.

Applicant argues that WO 94/26284 teaches a method of modifying TALL-104 cells by a short 18-hour treatment, and does not teach a process of amplifying TALL-104 cells, as presently claimed.

As noted above, WO 94/26284 teaches that the TALL-104 cell line is an immortal, permanently and rapidly growing cell line that can be expanded in vitro by culture in IL-2 to provide unlimited number of cells (see page 19 in particular). Thus, in contrast to Applicant's assertions, WO 94/26284 does teach that TALL-104 cells can be rapidly expanded and amplified by culture in IL-2. The fact that WO 94/26284 also teaches an additional method to modify TALL-104 cells after in vitro amplification is not relevant.

Applicant further argues that W0 94/26284 teaches that the TALL-104 cells originate by culture in antibiotic containing medium, while the instant claims specify an antibiotic free culture medium.

WO 94/26284 teaches that TALL-104 cells were originally established by O'Connor et al. by culture of peripheral blood cells in a medium containing antibiotics and various cytokines. However, WO 94/26284 goes on to teach that the maintenance of TALL-104 cells for the purposes of the described experiments, is performed by culture in medium supplemented with 10% fetal bovine serum (i.e. a medium without antibiotics, see page 26, paragraph 1). Thus, even though the TALL-104 cells originated by culture in antibiotic containing medium, it would have been obvious to use antibiotic free medium, since WO 94/26284 teaches that TALL-104 cells can be maintained by culture with medium containing only fetal bovine serum.

Applicant further argues that the LAK cells grown in a Cell Factory™ by Gambacorti-Passerini are different from TALL-104 cells, and that teachings regarding LAK cell cultures are not applicable to the amplification of TALL-104 cells.

As taught by WO 94/26284, LAK cells represent a heterogeneous population of cytotoxic cells. TALL-104 cells simply represent a clonal population of cytotoxic cells that are also found within the heterogeneous LAK cell population (see page 13 in particular). Moreover, both LAK cells and TALL-104 cells are grown in a nearly identical manner by suspension culture with IL-2. In fact, if anything, the process of growing

TALL-104 cells is easier and more reproducible compared to LAK cells, since TALL-104 cells are immortal and stable, thus avoiding some of the reproducibility problems encountered with growing LAK cells (see pages 19-20 in particular). Thus, the ordinary artisan would have had a reasonable expectation of success in applying the multi-chamber culture system used for growing LAK cells to grow TALL-104 cells.

Applicant further argues that Gambacorti-Passerini et al. only teach a process for the activation of LAK cells, and do not ensure amplification of LAK cell numbers.

Gambacorti-Passerini et al. teach that the culture method results in the proliferation of LAK cells (i.e. the amplification of LAK cells, see Table 5 and Fig. 1, in particular). Moreover, irrespective of the teachings of Gambacorti-Passerini et al., WO 94/262284 teaches that culture of TALL-104 cells with IL-2 leads to an unlimited in vitro amplification of the cells. Thus, the ordinary artisan would have a reasonable expectation of amplifying TALL-104 cells by culture with IL-2, even using the multi-chamber culture system described by Gambacorti-Passerini et al.

Applicant further argues that Tuyaerts et al. teach the amplification of typical adherent cells, which is not relevant to the amplification of TALL-104 cells, which are grown in suspension.

Tuyaerts et al. is cited in order to demonstrate what types of volumes might be used to grow cells in a multi-chamber stack, especially when the cell culture procedure requires multiple additions of cytokines to ensure the growth of the cells, as is the case with TALL-104 lymphocytes. Furthermore, while the precursor cells described by Tuyaerts et al. are initially adherent, the actual dendritic cells resulting from the culture are non-adherent cells (see page 139 in particular). Moreover, Gambacorti-Passerini et al. teach that cytotoxic lymphocytes can be grown in multi-chamber stacks in suspension cultures. Thus, the ordinary artisan would have a reasonable expectation of success in using a multi-chamber stack to grow suspension cells.

Applicant further argues that Tuyaerts et al. only teach adding an initial volume of 160 mls of medium/chamber to the multi chamber stack, while in contrast, the instant claims require a volume that is 1/6 to 1/10 of the volume capacity of the chamber. Applicant notes that the specification discloses that a 10 chamber stack has a volume

capacity of 2000 mls (i.e. 200 mls per chamber), and thus the claims are limited to adding only 20 to 33ml per chamber, rather than the 160 mls per chamber, as reported by Tuyaerts et al.

While the specification discloses on page 7 an example of a cell chamber having a final capacity of 2000 mls, this is not the volume capacity of all cell chambers. For example, as evidenced by the Nunc product information sheet, the **minimum** volume to be used in a 10 chamber cell factory is 2000 mls. Thus, 2000 mls is clearly not the maximum volume capacity of the Nunc Cell Factory™ used by the cited references.

Applicant further argues that the volume capacity calculations based on the overall external dimensions of the Cell Factory™ are not correct, since the Cell Factory™ is composed of several chambers which occupy some physical space. Applicant notes that the Nunc product information sheet discloses the culture area to be 6320 cm^2, which would result in a volume of 63.2 to 105 ml per chamber, as the 1/6 to 1/10 values required by the claims.

While it is true that the volume capacity of the cell factory will be somewhat less than that predicted using the external dimensions, Applicant's calculations are not correct. A two dimensional value (i.e. 6320 cm^2) cannot be extrapolated into a volume calculation, which requires 3 dimensions. As noted by Applicant, the Nunc product information teaches that the culture area of the cell factory is 6320 cm^2 (i.e. 632 cm^2) per chamber of a 10 chamber unit). A volume can be determined by multiplying this value by the actual height of each chamber. The total height of the 10 chambers is 190 mm (i.e. 19 mm per chamber). Even if it is assumed that as much as 20% of the total vertical height is lost due to the physical space occupied by the stacked chambers, the total volume of the stack would still be 9.6 liters. Thus, adding 160 mls per chamber, as made obvious by Tuyaerts et al., would still be 1/6 of the volume capacity of the cell factory. Moreover, it would have been obvious to optimize the initial volume used to inoculate the chamber to decrease the initial volume added, as noted above.

Applicant further argues that the cited references only teach addition of subsequent volumes of medium of the same type, and do not teach adding the same volume of medium, as recited in the amended claims.

It would have been obvious to optimize the volume added, and the amount recited in the instant claims is well within the purview of the ordinary artisan, as noted above.

2. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/26284, Gambacorti-Passerini et al., Tuyaerts et al., and Schumpp et al., as applied to claims 1, 5-8, 10-13, 15, 25-26 and 28 above, and further in view of U.S. Patent 6,491,678.

The combined teachings of WO 94/26284, Gambacorti-Passerini et al., Tuyaerts et al., and Schumpp et al. are discussed above.

They do not teach creating a sampling chamber in the frozen bags for the purpose of performing quality controls.

The '678 patent teaches a freezing bag that can be sealed to create sample chamber that can be detached without thawing for testing the suitability of the frozen cells (see column 3 in particular). The '678 patent teaches that the sample chamber can comprise up to 1 ml (see column 9 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to create a detachable sample chamber comprising up to 1 ml, as taught by the '678 patent, in the method of freezing the killer cells in bags, made obvious by WO 94/26284, Gambacorti-Passerini et al., Tuyaerts et al., and Schumpp et al. The ordinary artisan would have been motivated to do so, since the '678 patent teaches the detachable chamber can be used to test the suitability of frozen cells without having to thaw the frozen bag.

3. No claim is allowed.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 7am to 3:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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